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(54) Title: USE OF HYALURONIC ACID FOR PREPARING COMPOSITIONS FOR TREATING ORAL CAVITY APHTHAS

(57) Abstract: Use of hyaluronic acid as the sole active ingredient for preparing compositions in particular for topical use for treating
oral cavity aphthas.

USE OF HYALURONIC ACID FOR PREPARING COMPOSITIONS FOR TREATING ORAL CAVITY APHTHAS

FIELD OF THE INVENTION

The present invention relates to the use of hyaluronic acid for treating oral cavity aphthas.

STATE OF THE ART

Aphthas, better known as recurrent oral aphthous ulcerations (ROAU), are ulcerous pathologies of the oral mucosa which affect more than 20% of the population. The etiology of this ailment is yet to be defined. Aphthas are round or oval protuberant ulcers, surrounded by bright red areolas, on the smooth tissue of the mucosa. Almost all types of aphthas, including small ones, are capable of causing pain.

Of the susceptible individuals one in ten will have monthly episodes, whereas the majority have 3-4 episodes of new lesions per year occur. Untreated lesions in general last for 7-10 days and heal without leaving scars. In general, aphtha treatments are intended to ease symptoms, although many types of therapies for treating aphthas have been considered.

For example analgesics for topical use have been employed for relieving symptoms, and anti-inflammatories for reducing pathological changes, while anti-bacterials have been contemplated for controlling microbial contaminations and secondary infections.

Anti-bacterial agents include antibiotics (tetracycline) and antiseptics (clorhexidine).

Mouthwashes containing wide spectrum antibiotics have been able to reduce new ulcers, following a 10 day treatment. This effect is due to a reduced oral microflora thereby reducing the effects of a secondary infection.

However, antibiotics have a potentially undesirable mycotic effect and can give rise to allergic reactions.

Anti-bacterial mouthwashes can provide some benefit by controlling pain, reducing both the effects caused by a secondary infection and the duration of the ulcer. Clorhexidine can reduce the total number of days with ulceration, but has

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not been at all effective on the incidence or severity thereof. Furthermore, it frequently gives rise to colour changes on the teeth and tongue and upsets taste sensation.

Hyaluronic acid is a natural constituent of connective tissue.

EP-A1-0444492 describes the topical use of high molecular weight hyaluronic acid for treating inflammatory diseases of the oral cavity, such as gingivitis.

WO 0209637 discloses pharmaceutical compositions for the topical treatment of inflammatory diseases of the oral mucosa such as stomatitis, containing an association of hyaluronic acid, glycyrrhetic acid and polyvinylpyrrolidone

SUMMARY OF THE INVENTION

The Applicant has found that hyaluronic acid is able to effectively cure oral cavity aphthas.

In this respect, the Applicant has surprisingly found that hyaluronic acid is not only able to alleviate the symptoms and reduce the duration of ulceration, as well as the severity thereof.

An aspect of the present invention is therefore the use of hyaluronic acid for preparing compositions, in particular for topical use, for treating oral cavity aphthas.

DETAILED DESCRIPTION OF THE INVENTION

The compositions containing hyaluronic acid for use in accordance with the invention are preferably liquid, solid and/or semisolid preparations in the form of O/W (oil in water) and W/O (water in oil) emulsions, ointments and creams, pastes, gels, solutions, suspensions, dispersions, powders, tensiolytes, oleolytes, or any other rheological form suitable for use alone or in combination with the other forms, also in the form of tablets, pills, gums, or in the form of any other applicative solutions known in the art and suitable for topical use in the oral cavity.

Even more preferably, the topical compositions for use in accordance with the present invention are in the form of oral cavity gels, mouthwashes and sprays.

Preferably hyaluronic acid is in the form of the sodium salt. Hyaluronic acid has preferably a molecular weight of between 800,000 and 4,000,000, even more

preferably between 1,000,000 and 2,000,000.

The topical compositions of the present invention preferably contain hyaluronic acid in the form of the sodium salt at concentrations of between 0.01 and 10% by weight on the total weight of the composition, more preferably between 0.01 and 5% by weight.

Some illustrative but non-limiting examples of compositions for topical use based on sodium hyaluronate are given.

Composition 1: gel

Sodium hyaluronate average molecular weight 1,500,000:	0.240 w/w
Xylitol	7.500 w/w
Sodium carboxymethylcellulose	4.500 w/w
PEG 40 hydrogenated castor oil	1.000 w/w
Glyceryl monolaurate	0.700 w/w
Polycarbophil	0.800 w/w
Lactic acid (Pharm.)	0.060 w/w
Sodium lactate	0.100 w/w
EDTA	0.050 w/w
Sodium saccharinate	0.220 w/w
Flavour	0.500 w/w
Dichlorobenzylalcohol	0.500 w/w
Colorant CI 42090 (FD&C BLUE 1)	0.00012 w/w
Colorant CI 47005 (D&C YELLOW 10)	0.00028 w/w
Sodium hydroxide	to pH=6.5
Water	remainder to 100

Composition 2: mouthwash

Sodium hyaluronate average molecular weight 1,500,000:	0.025 w/w
Xylitol	7.500 w/w
PEG 40 hydrogenated castor oil	0.600 w/w
Polycarbophil	0.150 w/w
Lactic acid (Pharm.)	0.060 w/w
Sodium lactate	0.100 w/w

EDTA	0.050 w/w
Sodium saccharinate	0.018 w/w
Flavour	0.100 w/w
Dichlorobenzylalcohol	0.500 w/w
Polysorbate 20	0.800 w/w
Colorant CI 42090 (FD&C BLUE 1)	0.00012 w/w
Colorant CI 47005 (D&C YELLOW 10)	0.00028 w/w
Sodium hydroxide	to pH=6.5
Demineralized Water	remainder to 100
<u>Composition 3: spray</u>	
Sodium hyaluronate	0.100
w/w	
Xylitol	7.500 w/w
PEG 40 hydrogenated castor oil	0.500 w/w
Dichlorobenzylalcohol	0.500 w/w
Lactic acid (Pharm.)	0.060 w/w
Sodium lactate	0.100 w/w
EDTA	0.050 w/w
Sodium saccharinate	0.220 w/w
Flavour	0.200 w/w
PVA	0.050 w/w
Propylene glycol	4.000 w/w
Sodium hydroxide	to pH=6.5
Demineralized water	remainder to 100

CLINICAL STUDY**A) STUDY DESIGN**

This controlled study used a double blind, single centre, parallel group design to determine the efficacy of a gel formulation in relieving the symptoms in subjects with recurrent oral aphthous ulceration.

B) STUDY POPULATION**B1) Number of Subjects**

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The investigator enrolled a sufficient number of subjects in the study to achieve a study population of 120 evaluable subjects (60 in each group) with ROAU.

B2) Subject-Selection Criteria

Inclusion Criteria To be eligible for study participation the subject had to meet the following criteria:

- The subject must be between 18 and 65 years of age
- A history of ROAU > 2 times per year
- Current aphthous ulcer/ulcers present for < 3 day

B3) Exclusion Criteria

Any of the following conditions excluded subjects from eligibility for study participation:

- Patients with underlying white blood cell disorder
- Patients taking systemic hemotherapy, immunosuppressants, or who suffer from drug-related recurrent aphthous ulceration
- Patients suffering from malignant disease
- Patients with uncorrected dietary defect
- Pregnant or breast feeding women
- A history of sensitivity of mouthwashes

B4) Prohibited/Allowable Medications

Prohibited Medications

- Any topical or systemic treatment for ROAU including steroids and vitamins B1 and B6 other than study treatments
- Antiseptic mouthwashes
- Systemic chemotherapy, immunosuppressants
- Rx or OTC nonsteroidal anti-inflammatory drugs including, but not limited to aspirin, diclofenac, diflunisal, etodolac, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, or sulindac.

Allowable Medications

- Any medication not specifically prohibited
- Paracetamol

C) STUDY METHODOLOGY

Subjects were recruited from an existing group of patients with ROAU who have been screened for known causative factors or when they present as new patients to the clinic. Existing patients or patients attending screening who do not have a current ulcer will be asked to contact the clinic at the time of onset of their next aphthous ulcer.

C1) Clinic Visit 1 (Day 1): Screened subjects meeting the selection criteria for the study described had the study explained to them and if they agreed to participate signed an informed consent form. They will be allocated a subsequent subject number. The subjects demographic history and history of ROAU were recorded together with details of their current episode of aphthous ulceration including the time and date of onset, number, size and position of mouth ulcers.

The study nurse explained to the subjects how to fill out the 10 cm visual analogue scale (VAS) used to score their level of discomfort or soreness arising from their mouth ulcer. Subjects recorded their discomfort from their ulcer prior to gel application (baseline). They applied the gel to the ulcerated area under supervision with 1-2 ml of their assigned gel having one of the following two composition:

Product name	Ingredients
Hyaluronic Acid Gel 0.2%	Aqua, xylitol, cellulose gum, alcohol, PEG-40, Hydrogenated castor oil, sodium hyaluronate, Polyvinyl alcohol, polycarbophil, Dichlorobenzyl alcohol, aroma flavouring CI 40290
Placebo	Aqua, xylitol, cellulose gum, alcohol, PEG-40, Hydrogenated castor oil, Polyvinyl alcohol, polycarbophil, Diclorobenzyl alcohol, aroma flavouring

Subjects recorded their discomfort immediately after application and at 5, 10, 15, 20, 30, 45 and 60 minutes. The time of gel application will be recorded in the CRF and the subjects log diary. A stopwatch was used to record time measurements.

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The subject will be supplied with sufficient tubes of the gel to take home. The study nurse instructed the subject how to fill out a log diary. The subject continued to record their VAS scores in their log diary at 2, 3 and 4 hours postgel application. The subjects will apply the gel again after their evening meal and record their VAS score 1 hour post application.

Appendix A; Time table of Visits and Procedures

C2) Day 2-7

Subjects continued to apply the gel at home 2 to 3 time daily, after breakfast and after their evening meal (and 1 other time during the day, if desired) from days 2-7, even if their ulcer has healed. VAS scores was recorded in the subjects' log diaries 1 hour post application in the morning and evening. Subjects recorded the severity of their mouth ulcers, any unpleasant effects of their study treatment and the severity of their mouth ulcers. Any new ulcers occurring was recorded in their log diaries.

C3) Clinic Visit 2 (Day 8):

Subjects returned to the clinic to review their completed log diaries with the study nurse and return remaining study material. They were asked to score their overall assessment of the gel on a 5 point scale. Subjects will be questioned about the occurrence of any adverse events.

Information obtained relating to adverse events were recorded on the associated pages of the CRF. The size, number and position of lesions present on day 8 were recorded on the CRF.

The VAS entries on each subjects log diary were measured and transcribed to the associated pages of the CRF.

C4) Efficacy Assessments

Following entry to the study, the study nurse recorded the subject's demographic details and examined the subject to determine the size, number and position of ulcers and record time of onset of ulcer.

C5) Primary Efficacy Parameter

Subjects recorded their discomfort/soreness scores on a 10 cm visual analogue scale (VAS).

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The boundaries of the scales were "worst possible" and "no soreness".

Scores were completed at baseline and at 0, 5, 10, 15, 20, 30, 45 and 60 minutes post initial application. The gel application and completion of scores was done under supervised conditions in the Clinic. At the end of 60 minutes, the subjects continued to apply the gel at home 2 to 3 times daily and they were asked to record discomfort/soreness on the same VAS twice daily an hour after the morning and evening applications.

Two parameters were extrapolated from the serial VAS completed in the first hour:

- a) Time in minutes to the maximum reduction in discomfort/soreness following dosing with the gel.
- b) Serial VAS recorded in the first hour was compiled into a graph of discomfort soreness (mm) versus time (minutes). The area under the graph was measured using the trapezoidal method and recorded as AUC (0-60 minutes). This provided an overall assessment of each subjects discomfort/soreness experience throughout the initial observation period.

C6) Secondary Efficacy Parameter

At the end of the 7 day investigation period, subjects were asked if they have had any ulcer free days and their overall assessment of the gel based on the following scale:

Very good Good Moderate Poor Very Poor

D) RESULTS

In this randomized blind clinical study it was evidenced that if compared to placebo composition the gel composition containing hyaluronic acid proved able to reduce significantly the number of ulcers already in the fifth day, and also evidenced an overall beneficial effect in every investigated ROAU symptomatology.

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CLAIMS

1. Use of hyaluronic acid for preparing compositions for the treatment of oral cavity aphthas, wherein hyaluronic acid is the sole active ingredient.
2. Use as claimed in claim 1 wherein the hyaluronic acid is in the form of sodium salt.
3. Use as claimed in claim 2 wherein said compositions are suitable for topical application.
4. Use as claimed in claim 3 wherein said compositions for topical use contain sodium hyaluronate in concentrations between 0.01 and 10% by weight on the total weight of the composition.
5. Use as claimed in claim 4, characterised in that said concentration is between 0.01 and 5% by weight on the total weight of the composition.
6. Use as claimed in any one of claims 1-5, characterised in that said average molecular weight is between 800,000 and 4,000,000.
7. Use as claimed in any one of claims 1-5, wherein said average molecular weight of the hyaluronic acid is between 1,000,000 and 2,000,000.

INTERNATIONAL SEARCH REPORT

National Application No

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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/715 A61P17/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 972 906 A (FALK RUDOLF EDGAR ET AL) 26 October 1999 (1999-10-26) page 1, paragraph 2 – paragraph 3 column 2, line 26 – line 40 column 5, line 35 – line 50	1-5
X	US 2002/183278 A1 (BRAGUTI GIANLUCA ET AL) 5 December 2002 (2002-12-05) paragraph '0002! paragraph '0017! claims 1,54,55	1-7 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>RUSSELL A L: "PARALLELISM BETWEEN CUTANEOUS AND MUCOSAL PATHOLOGY. A NEW TEST BEDFOR AT 2101 (3% DICLOFENAC ACID IN 2.5% HYALURONAN)"</p> <p>ROYAL SOCIETY OF CHEMISTRY. ROUND TABLE SERIES, ROYAL SOCIETY OF MEDICINE SERVICES, LONDON, GB,</p> <p>vol. 40, 1 December 1995 (1995-12-01),</p> <p>pages 125-131, XP000603132</p> <p>ISSN: 0268-3091</p> <p>page 125, paragraph 2 – paragraph 6</p> <p>page 129, paragraph 2</p> <p>-----</p>	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

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